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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/808,314
Filing Date: March 14, 2001
Appellant(s): NELSON ET AL.

Laura J. Zeman
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed January 8, 2007 appealing from the Office action mailed August 9, 2005.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

Papac et al., "Direct Analysis of Affinity-Bound Analytes by MALDI/TOF MS", Anal. Chem. 1994, 66, pp. 2609-2613.

Gaskell, Simon "Quantifiction of steroid conjugates using fast atom bombardment mass spectrometry" Steroids, 1990, Vol. 55, pp. 458-462.

Chiabrando et al., "Quantitative Profiling of 6-Ketoprostaglandin F 2,3, Dinor-6Ketoprostaglandin" Journal of Chormatography, 495 (1989), pp 1-11.

3,770,337 MERREN 11-1973

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein

were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 31-33, 35 and 36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Papac et al (Direct Analysis of Affinity-Bound analytes by MALDI/TOF, Anal. Chem. 1994, 66, 2609-2613) in view of Gaskell (Quantiication of steroid conjugates using fast atom bombardment mass spectrometry, steroids, 1990, vol. 55, pages 458-462).

Papac et al disclose a method for the Mass spectral identification and detection of analytes separated by immunoaffinity chromatography (abstract). Papac et al disclose antibody immobilized to agarose beads and used as affinity columns (p. 2611, Results and Discussion section and Fig. 2). Papac et al disclose combining a specimen with the beads to capture antigen present in the sample (post-combination affinity reagent). Papac et al disclose washing to remove any unbound antigen. Papac et al disclose that the sample is mixed with the beads and centrifuged and supernatant removed. Papac et al discloses that a matrix containing formic acid was added and the supernatant was tested by MALDI/TOF mass spectrometry (single dimension mass spectrometeromic analysis) (p. 2611, col 1 & p. 2613, col 2). Papac et al disclose determining the analyte by m/z (mass to charge ratio).

Papac et al (Anal Chem.) differ from the instant invention in failing to teach the specimen is combined with an internal reference species (IRS) of known concentration prior to the capturing and isolation step wherein both the analyte and the IRS are captured and isolated. Papac et al also fails to teach quantifying the analyte.

Gaskell discloses quantifying an analyte, where a deuterated internal standard is added to a sample, which is then mixed with a solid phase incorporating bound antiserum for isolating the analyte and internal standard. Gaskell discloses that for quantification of the analyte, the analyte and internal standard are compared to a standard curve (p. 460). Gaskell discloses that the standard curve was obtained by analyses of standard mixtures of the analyte and the analyte analog. Gaskell further discloses that the addition of an internal standard provides for precise and accurate data (p. 459) and provides for the quantification of an analyte.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate an internal standard and affinity reagents and also develop a standard curve for quantification analyses, as taught by Gaskell, into the method of Papac et al (Anal. Chem). Because Gaskell teaches that the addition of an internal standard would provide for precise and accurate data and for the quantification of an analyte of interest. Therefore, one of ordinary skill in the art would have a reasonable expectation of success incorporating an internal standard and affinity reagents as taught by Gaskell into the method of Papac et al.

Claims 37-40 and 42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Papac et al in view of Gaskell as applied to claims 31-33, 35 and 36 above, and further in view of Chiabrando et al (Journ of Chromatography 495 (1989) 1-11).

See above for teachings of Papac et al and Gaskell.

Papac et al and Gaskell differ from the instant invention in failing to teach combining a plurality of distinctive internal reference species to the sample.

Chiabrando et al disclose the step of adding multiple deuterated internal standards to a sample and also the use of immobilized antibodies to capture and isolate the analytes and internal standards (internal reference) (p. 1). Chiabrando et al discloses that this provides for the simultaneous measurement of analytes and their metabolites (p. 2, first column).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate multiple internal standards as taught by Chiabrando et al into the modified method of Papac et al because Chiabrando et al discloses that this provides for the simultaneous measurement of different analytes and their metabolites.

Claims 44-46 and 48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Papac et al and Gaskell in view of Chiabrando et al as applied to claims 31-33, 35-40 and 42 above, and further in view of Merren (US 3,770,337).

See above for teachings of Papac et al., Gaskell, and Chiabrando et al.

Papac et al (Anal. Chem.), Gaskell and Chiabrando et al differ from the instant invention in failing to specifically teach interpolating the analyte species mass spectrometric response to the IRS's mass spectrometric response.

Merren teaches the addition of reference substance which provides a spectrum containing peaks at several known mass-to-charge ratios. Merren teaches that the reference spectrum is accurately correlated with the spectrum of the unknown substance, therefore the reference peaks act as accurate markers forming a calibrated scale from which the mass-to-charge ratios of peaks of the unknown substance is interpolated. Merren teaches that this provides a method for combining signals representative of the simultaneous spectral analysis of two substances, thereby permitting single channel processing of the combined signal (col 1, lines 53 – col 2, lines 19.

It would have been obvious to one or ordinary skill in the art at the time the invention was made to interpolating the analyte species and the reference species as taught by Merren into the modified method of Papac et al (Anal. Chem.) because Merren shows that this provides a method for combining signals representative of the simultaneous spectral analysis of two substances, thereby permitting single channel processing of the combined signal.

Double Patenting

Claims 31 and 37 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 31-50 of copending Application No. 09/024,988. Although the conflicting claims are not identical,

they are not patentably distinct from each other because although the claims of application this instant 09/808,314 application do not require that the IRS is modified analyte with shifted molecule weight as independent claim 31 in application 09/024,988 one of ordinary skill would recognize that the more narrow claims of 09/024,988 would encompass the broader claims of 09/808,314.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

(10) Response to Argument

Appellant argues that unlike Appellants' claimed invention, the Papac reference analyzes a predetermined analyte and not the identification and amount of analyte present in a biological or physiological specimen. This is not found persuasive because although the analyte is predetermined the process steps of Papac perform the identification by determining the peaks as Figure 2. Further, the Examiner has not relied upon Papac for determining the amount but rather has relied upon Gaskell for teaching that it is known in the art to use internal reference species in mass spectrometry assays and teaches that this provides for precise and accurate data for quantification of analytes. Further, it is also noted that there is nothing in the claims that recites a biological or physiological specimen. The instantly recited claims merely require a specimen, it is noted that the features upon which applicant relies (i.e. biological or physiological specimen) are not recited in the rejected claims(s). Although the claims are interpreted in light of the specification, limitations from the specification

are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Appellant further argues that in Papac, aliquots of beads containing the predetermined analyte are removed from the column for performing MALDI/TOF analysis. Appellant directs the Examiner's attention to page 2611, column 1, first paragraph. Appellant states that the discussion under mass spectrometry on page 2611, first paragraph of the Papac reference, merely describes how the same aliquots of beads containing the known analytes were prepared for performing mass spectrometry. Appellant states that this is clearly confirmed in the results and discussion section which states: "purification is necessary before binding the antibody to the affinity support. To accomplish this purification, Cytochrome C was first bound to the affinity support (experimental section). The crude antibody solution was passed through the column, and a 1 microliter aliquot of the column was used to acquire the MALDI/TOF spectrum shown in Figure 1A". Appellant states that in the Appellants' claimed invention, a released analyte species is detected using mass spectrometer to determine whether the analyte species is present in the physiological specimen. This is not found persuasive because first it is not clear why Appellant is referring to page 2611, column 1, first paragraph. The Examiner has relied upon Papac for the teachings disclosed on page 2611, results and discussion section second column and Figure 2. Further, if Appellant arguments are directed to the statement that Appellants' claimed invention is directed to "a released analyte species". There is nothing in the claim which recites "a released analyte species". The claim recites "capturing and isolating". Papac

clearly teaches on page 2611 results and discussion section second column and Figure 2, that immobilized mabE8 on agarose beads captures cytochrome c and that the column of beads is washed to remove any unbound cytochrome c. Thus, Papac is teaching capturing the analyte and separating unbound cytochrome c from cytochrome c bound to the agarose beads containing the anlyte. Thus, Papac is teaching isolation. In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., a release analyte) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Further, as stated above physiological specimen is also not recited in the instant claims. Appellant further states that Papac fails to disclose any quantification. Examiner agrees that Papac does not teach quantification (see the 103 rejection above). However, Gaskell teaches that it is known in the art to use internal reference species in mass spectrometery assays and teaches that this provides for precise and accurate data for quantification of analytes.

Appellant argues that the Gaskell reference specifically states that "the success of the detection procedure was dependent on both the selectivity of tandem MS detection and on the achievement of a sufficiently "clean" biologic extract by Immunoadsorption." Accordingly, the Gaskell reference cited by the Examiner actually teaches away from the instantly claimed invention by using tandem MS for quantification. Appellant states that different mass spectrometric measurements were taken of similar portions of the

same serum extract and compared. In contrast, Appellants' instantly claimed invention, the analyte and IRS are measured using MS in a single measurement. Accordingly, it would not have been obvious to one of ordinary skill in the art to incorporate the method disclosed in Gaskell into the method of Papac to arrive at Applicants' claimed invention because Appellants' claimed invention would then require tandem MS and Appellants' claimed invention requires single dimension MS. This is not found persuasive because as stated in the previous office actions the Examiner has not relied upon Gaskell for teaching tandem MS, but rather has relied upon Gaskell for teaching that it is known in the art to incorporate internal references into a sample for the quantification of an analyte. The primary reference (Papac et al) clearly teaches the use of MALDI/TOF (single dimension) (same as used by Applicant) in a method for the detection of analyte and the secondary reference (Gaskell) teaches the incorporation of an internal standard in methods to provide for the quantification of an analyte. Also, as stated in the previous office actions, it would have been obvious to incorporate an internal standard and also develop a standard curve for quantification analyses as taught by Gaskell, into the method of Papac et al (Anal Chem). Because Gaskell teaches that the addition of an internal standard provides for precise and accurate data and provides for the quantification of an analyte of interest. Thus, Examiner has not relied upon Gaskell for the steps of quantification but rather has relied upon Gaskell for teaching that it is known in the art to use internal standards to develop a standard curve which provides for the quantification of an analyte. Therefore, one of ordinary skill in the art would understand that the incorporation of a standard curve of Gaskell in the method of Papac

et al provides for the quantification of an analyte. The combination of Papac et al and Gaskell would include a single dimension mass spectrometric process for quantifying an analyte.

Appellant argues that the Papac reference fails to disclose the use of combining an internal reference species with a specimen, capturing and isolating an analyte and the internal reference species contained in the specimen and quantifying the analyte using single dimension mass spectrometric analysis to resolve signals for the analyte and the internal reference species to determine the amount of the captured analyte and that the Gaskell reference fails to disclose using single dimension mass spectrometry and instead requires using tandem mass spectrometry for detecting an analyte and internal standard and for quantifying the analyte. This is not found persuasive because of reasons stated above the combination of Papac and Gaskell would encompass these claimed limitations. Appellant further argues that Chiabrando discloses a method which utilizes gas chromatography-mass spectrometry and Chiabrando fails to disclose the use of single dimension mass spectrometry to analyze and quantify an analyte. This is not found persuasive because the Examiner has not relied upon Chiabrando for teaching these limitations but rather has relied upon Papac and Gaskell for teaching these limitations. The examiner has relied upon Chiabrando for teaching that it is known in the art to combine a plurality of distinctive internal reference species to a sample. Also, in response to appellant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413,

208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Appellant argues that Merren fails to disclose single dimension mass spectrometric analysis of an analyte and an internal reference species using a standard single beam mass spectrometer. This is not found persuasive because Examiner has not relied upon Merren for teaching single dimension mass spectrometric analysis but rather has relied upon the combination of Papac et al. Gaskell and Chiabrando for teaching this limitation. Examiner has relied upon Merren for teaching interpolating the analyte species mass spectrometric response to the IRS's mass spectrometric response. Therefore, it is the Examiner's position that the combination of references is proper and reads on the instantly recited claims.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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